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MEDICAL POLICY

MINIMALLY INVASIVE PROCEDURES FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD)

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Bariatric Surgery

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COVERAGE RATIONALE

Endoscopic therapies are unproven for the treatment of gastroesophageal reflux disease (GERD).

Endoscopic therapies include:

1. Radiofrequency energy
   - Stretta System

2. Endoscopic plication or suturing
   - Bard EndoCinch Endoscopic Suturing System
   - Endoscopic Suturing Device (ESD)
   - Surgical Endoscopic Plication System (EPS)

- EsophyX™ System with SerosaFuse™ Fastener (transoral incisionless fundoplication procedure)

3. Injection or implantation techniques
   - Gatekeeper Reflux Repair System
   - Plexiglas (polymethylmethacrylate [PMMA]) procedure
   - Durasphere®

The safety and efficacy of endoscopic therapies for the treatment of GERD have not been established in the published medical literature. Current studies are generally of small to moderate size, lack adequate control or comparison groups, and provide only short-term follow-up. Well-designed clinical trials with long-term follow up are required to establish that endoscopic therapies benefit health outcomes in patients with GERD by eliminating symptoms, preventing recurrence of symptoms or progression of disease, healing esophagitis, and reducing or eliminating the need for pharmacologic therapy.

The LINX™ Reflux Management System is unproven for the treatment of GERD. The safety and efficacy of this system has not been established in the peer-reviewed medical literature. Available studies are hampered by a number of limitations, including small study size, lack of statistical power, lack of controls or comparators, and lack of long-term follow-up.

See the Medical Policy titled Bariatric Surgery for information regarding transoral endoscopic surgery (such as transoral gastroplasty [TOGA®], StomaphyX, and Restorative Obesity Surgery, Endoluminal [ROSE] procedure) for the treatment of obesity.

BACKGROUND

Gastroesophageal reflux disease (GERD) is a condition that is characterized by either a weak or dysfunctional lower esophageal sphincter that results in partially digested food from the stomach to flow back into the esophagus, a process known as reflux. Persistent GERD may lead to esophageal damage or other serious conditions, such as severe esophagitis, strictures, Barrett's metaplasia, and adenocarcinoma of the esophagus.

Initial treatment of GERD usually involves over-the-counter (OTC) antacids, OTC histamine-2-receptor antagonists (H_2RAs; also called H_2 blockers), and proton pump inhibitors (PPI), all of which generally provide effective control of symptoms, depending on the severity of the disease and clinical response. For patients who wish to discontinue use of these medications due to concern of long term side effects or for patients whose GERD is refractory to pharmacologic treatment, an open or laparoscopic Nissen fundoplication may be considered. However, some patients may not be suitable candidates given the invasiveness and risks associated with surgery. As a result, minimally invasive procedures, including endoscopic or endoluminal therapies and laparoscopic approaches, have been proposed as alternative treatment methods to improve the function of the lower esophageal sphincter (LES), with the objective of eliminating symptoms, healing esophagitis, preventing recurrence of symptoms or progression of disease, and reducing the need for lifelong pharmacologic therapy.

Minimally invasive approaches used to treat GERD, including the following:

- Radiofrequency energy: The Stretta procedure administers radiofrequency (RF) energy via endoscopic needles placed in the tissues surrounding the lower esophageal sphincter. The RF energy heats this neighboring tissue, creating thermal lesions. Submucosal scarring forms as the lesions heal, causing shrinkage and tightening around the LES. Theoretically, these changes to the esophageal sphincter reduce acid reflux by restoring the natural barrier function of the LES, and reducing the spontaneous regurgitation caused by transient relaxation of the LES (SAGES, 2012).
- Endoscopic plication or suturing: The Bard EndoCinch and the Endoscopic Suturing Device (ESD), involves endoscopic suturing, allows for the placement of proximal to the LES, and the NDO Endoscopic Plication System, also known as the NDO Plicator

System, places a full-thickness transmural plication near the gastroesophageal junction under direct endoscopic visualization. EsophyX is an endoluminal therapeutic option that uses a trans-oral and fastener deploying device. The device is passed into the stomach, where it deploys a series of full-thickness fasteners to create a neogastroesophageal valve. The EsophyX device creates a transoral incisionless fundoplication (TIF). Endoscopic plication procedures that are performed through the mouth or anus (natural orifice) are examples of natural orifice surgical procedures.

- Injection or implantation techniques include the following:
  - The Plexiglas (polymethylmethacrylate [PMMA]) procedure involves injection of an inert polymer material into the submucosa of the proximal lower esophageal sphincter zone to provide bulking support to the sphincter and decrease transient relaxation of the lower esophageal sphincter (tLESRs).
  - The Gatekeeper Reflux Repair System utilizes a soft, pliable, expandable prosthesis made of a polyacrylonitrile-based hydrogel. The prosthesis is implanted into the esophageal submucosa, and with time, the prosthesis absorbs water and expands, creating bulk in the region of implantation. These agents are not commercially available in the United States.
  - Another bulking agent, pyrolytic carbon-coated beads (Durasphere®), is being evaluated for treatment of GERD. Durasphere is approved by the U.S. Food and Drug Administration (FDA) as a submucosal urethral bulking agent. Use of this product for esophageal reflux would be considered off-label use.
  - The LINX™ Reflux Management System is an implant that consists of a ring that fits around the esophagus and is intended to prevent reflux of bile and acid from the stomach into the esophagus. According to the company Web site, the LINX system is a small flexible band of interlinked titanium beads with magnetic cores. The magnetic attraction is intended to help the (LES) resist opening to gastric pressures, preventing reflux from the stomach into the esophagus. A surgeon uses a laparoscopic incision to implant the device around the patient's esophagus just above the stomach while the patient is under general anesthesia.

Specific manipulation of the endoscopic and laparoscopic devices is a surgical skill requiring extensive training and experience. Performance of these procedures requires a physician with the training and experience in the particular endoscopic system in use.

CLINICAL EVIDENCE

Radiofrequency Energy (Stretta System)

Arts et al. (2012) conducted a double-blind randomized cross-over study of Stretta and sham treatment. Patients underwent two upper gastrointestinal endoscopies with 3 months interval, during which active or sham Stretta treatment was performed in a randomized double-blind manner. In all, 22 GERD patients (17 females, mean age 47±12 years) participated in the study; 11 in each group. Initial sham treatment did not affect any of the parameters studied. Three months after initial Stretta procedure, no changes were observed in esophageal acid exposure and lower esophageal sphincter (LES) pressure. In contrast, symptom score was significantly improved and gastro-esophageal junction (GEJ) compliance was significantly decreased. Administration of sildenafil, an esophageal smooth muscle relaxant, normalized GEJ compliance to pre-Stretta level, arguing against GEJ fibrosis as the underlying mechanism. The authors concluded that Stretta improved GERD symptoms and decreased GEJ compliance. According to the authors, the limitation of this study was reflux evaluation did not include impedance monitoring. The study was also limited by a small patient population, short follow-up, and lack of comparison to other surgical alternatives.

In a RCT, 36 patients were randomized into three groups. In group A, 12 patients underwent a single session Stretta procedure (Aziz et al., 2010). In group B, 12 patients under went a sham Stretta procedure (mirror of the active procedure in all aspects except there was no deployment of the electrodes). In group C, 12 patients underwent a single Stretta treatment followed by repeat

Stretta if GERD health-related quality of life (HRQL) was not 75% improved after 4 months. At 12 months, the mean HRQL scores of patients no longer on medications, the lower esophageal sphincter (LES) basal pressure, the 24-hr pH scores, and the PPI daily dose consumption were significantly improved from baseline in both Stretta groups. The double Stretta was numerically but not significantly better than the single Stretta for mean HRQL, mean 24 h pH, mean LES pressure, and PPI use. Seven patients in the double Stretta treatment group reported normal HRQL scores at 12 months compared with 2 patients in the single-treatment group. The sham group patients had a small but statistically significant decrease in their daily PPI dosages and mean HRQL scores. The investigators concluded that the Stretta procedure significantly reduced HRQL associated with GERD, use of PPI drugs, esophageal acid exposure, LES pressure, and grade of esophagitis compared with the sham procedure. The double Stretta therapy had numerically superior outcomes for most parameters and a significantly more frequent normalization of HRQL scores compared with the single Stretta group. According to the investigators, the Stretta procedure is partially effective for the treatment of GERD symptoms. Double Stretta therapy has better efficacy than single therapy, but has greater side effects. The investigators also noted that antireflux surgery (fundoplication) has a higher success rate than that of Stretta. Furthermore, a more prolonged effect is found with antireflux surgery. The conclusions of this study are limited by small sample size and lack of comparison to other surgical alternatives.

Investigators of a small randomized, double-blind, sham-controlled, multicenter trial reported that radiofrequency energy delivery significantly improved GERD symptoms and QOL compared with the sham procedure, but it did not decrease esophageal acid exposure, LES pressure, or medication use at 6 months. Nevertheless, responders, with a > 50% reduction in HRQL score, experienced significant median decreases in 24-hour acid exposure time. In addition to a 13% dropout rate, a greater-than-anticipated number of sham patients discontinued their medications, resulting in a study that was underpowered (Corley et al., 2003).

In another RCT, Coron et al. (2008) compared radiofrequency and a PPI in PPI-dependent patients. Patients were randomly allocated to either RF or PPI regimen alone. The primary endpoint, evaluated at 6-months, was defined as the possibility for the patient to stop or to decrease PPI use to <50% of the effective dose required at baseline. In the radiofrequency group, 18/20 patients stopped (n = 3) or decreased (n = 15) PPI use compared to eight of 16 in the PPI group. None of the control patients could stop PPI. HR-QOL scores were not significantly different between groups. No significant change in oesophageal acid exposure (OAE) was noted between baseline and 6-months after radiofrequency treatment. The investigators concluded that in a majority of patients, PPI therapy cannot be completely stopped. Furthermore, the efficacy of RF does not seem to be related to a decrease in OAE.

In a controlled trial, Jeansonne et al. (2009) compared the effectiveness of endoscopic full-thickness plication (FTP) and endoscopic radiofrequency treatments for patients with GERD. Follow-up data was obtained for 63 patients (mean follow-up was 6 months). Outcome measures included comparison of medication use, symptom scores, and pH values at baseline and follow-up. In the RF group, patients with moderate to severe heartburn decreased from 55% to 22%, and PPI use decreased from 84% to 50%. Decreases were also seen for dysphagia, voice symptoms, and cough. The pH values were unchanged. In the FTP group, patients with moderate to severe heartburn decreased from 53% to 43%, and PPI use decreased from 95% to 43%. Percentage of time that the pH was less than 4 decreased from 10.0% to 6.1%. Decreases were also seen for regurgitation, voice symptoms, and dysphagia. According to the investigators, RF and FTP both resulted in a decrease in both PPI use and in scores for voice symptoms and dysphagia. In addition, RF resulted in decreased heartburn and cough, while FTP resulted in the most dramatic reduction in regurgitation. The investigators concluded that both procedures are effective, providing symptomatic relief and reduction in PPI use. For patients whose chief complaint is regurgitation, FTP may be the preferred procedure. Study limitations included lack of randomization, small sample size, and short follow-up.

Numerous non-randomized and non-comparative cohort studies evaluated radiofrequency energy for the treatment of GERD (Dughera et al., 2011; Liu et al., 2011; White et al., 2009; Dundon et al., 2008; Noar and Lotfi-Emran et al., 2007; Reymunde and Santiago, 2007; Lutfi et al., 2005; Richards et al., 2003; Triadafilopoulos et al., 2002; Triadafilopoulos et al., 2001). The body of evidence is of low quality due to overall weaknesses in study design, including lack of comparison groups, lack of randomization, and small patient populations.

Torquati et al. (2007) conducted an evidence-based systematic review of the literature of FDA-approved modalities of endoluminal treatment of GERD. Study authors concluded that the methodological quality of most of the included studies was average. The authors stated that there is grade 1b (individual randomized trial) and 2b (individual cohort study) evidence demonstrating that the Stretta procedure is effective in reducing GERD symptoms at short- and mid-term follow-up. However, in the majority of the studies analyzed, the procedure did not significantly reduce acid exposure in the distal esophagus.

Summary
Additional well-designed clinical trials comparing radiofrequency energy with other surgical alternatives are needed to determine the efficacy and long-term effectiveness of radiofrequency energy. The current body of evidence is of low to moderate quality with several study limitations, including lack of generalizability and lack of sufficient follow-up data. There are persistent questions regarding the safety of radiofrequency energy over the long term.

Endoscopic Plication or Suturing

EndoCinch
Schwartz et al. (2007) conducted a single-center, double-blind, randomized, sham-controlled trial of endoscopic gastroplication by the Endocinch suturing system in 60 patients. Patients with GERD were randomly assigned to three endoscopic gastroplications (n = 20), a sham procedure (n = 20) or observation (n = 20). The research nurse and patients in the active and sham groups were blinded to the procedure assignment. After 3 months, open-label active treatment was offered to all patients. At 3 months, the percentage of patients who had reduced drug use by ≥50% was greater in the active treatment group (65%) than in the sham (25%) or observation groups (0%). The active treatment effects on PPI use, symptoms and quality of life persisted after 6 and 12 months of open-label follow-up (n = 41), but 29% of patients were retreated in this period. The investigators concluded that endoscopic gastroplication, using the Endocinch device, reduced acid-inhibitory drug use, improved GERD symptoms, and improved the quality of life at 3 months compared with a sham procedure with durable effects up to 12 months. However, the reduction in oesophageal acid exposure was not significantly different between treatment and sham groups.

In a randomized, placebo controlled study by Montgomery et al. (2006), 46 patients with GERD requiring regular use of PPIs were enrolled to evaluate the effects of the EndoCinch plication technique. Patients were randomized to the EndoCinch plication technique or a sham procedure. Reflux-specific symptoms and use of PPIs (total intake, as well as number of patients not taking PPIs) significantly improved in the treatment group compared with the sham control group at 3 months of follow-up. Gastro-esophageal endoscopy showed that 71% and 67% of sutures remained at 3 and 12 months, respectively. The authors concluded that although some short-term positive effects were achieved, there were no significant differences between the treatment and control groups after 12 months. Additionally, the lack of reduction of esophageal acid exposure suggests that the EndoCinch plication technique is not recommended for use in clinical practice. Researchers posit that the lack of long-term effects is primarily due to detachment of the sutures in about 30% of patients.

In a RCT, endoluminal gastroplasty (EndoCinch) was compared with polymer injection (Enteryx). The study included 51 patients dependent on PPI therapy. Twenty-six patients were assigned to EndoCinch treatment, 23 patients received Enteryx implantation, and 2 patients dropped out

before applying endoscopic therapy. At 6 months, PPI therapy could be stopped or dosage was reduced by ≥ 50% in 20 of 26 EndoCinch-treated patients and in 20 of 23 patients treated by Enteryx. The authors concluded that EndoCinch and Enteryx seem to be equally successful in the treatment of GERD by significantly reducing the PPI dosages, and also improving symptoms of patients (Domagk et al., 2006). Conclusions regarding long-term health outcomes could not be made based on the short-term follow-up duration of this study.

Torquati et al. (2007) conducted a systematic review of endoluminal therapies for GERD, including EndoCinch. The authors identified evidence demonstrating that EndoCinch plication is effective in reducing GERD symptoms in the short term. However, they noted that the procedure does not significantly reduce the acid exposure in the distal esophagus.

Other clinical trials for EndoCinch are limited to observational case series that do not allow for conclusions about durability and long term effectiveness (Filipi et al., 2001; Paulssen and Lindsetmo, 2008; Ozawa et al., 2009).

Endoscopic Plicator or Suturing
In a randomized, single-blind, prospective, multicenter trial by Rothstein et al. (2006), 159 patients were selected to either undergo endoscopic full-thickness restructuring of the gastric cardia with transmural suture (n=78) or a sham procedure (n=81) to determine the effectiveness of endoscopic full-thickness plication for the treatment of GERD. Group assignments were revealed following the 3-month evaluation. By intention-to-treat analysis, at 3 months, the proportion of patients achieving ≥50% improvement in GERD-HRQL score was significantly greater in the active group compared with the sham group. Complete cessation of PPI therapy was higher among patients in the active group than in the sham group. However, the median percent time that pH < 4 was not significantly improved between the active and sham group. Between-group analysis revealed the active therapy was superior to sham treatment in improving the median percent time that the pH value was < 4. The authors concluded that endoscopic full-thickness plication was effective in reducing GERD symptoms and PPI use compared with a sham procedure. Additional studies are needed to evaluate the durability of endoscopic full-thickness plication for the treatment of GERD.

In a RCT, Antoniou et al. (2012) evaluated the effectiveness of endoscopic plication and laparoscopic fundoplication in terms of QOL and symptom control. A total of 60 patients with documented GERD were randomly assigned to undergo either endoscopic plication or laparoscopic fundoplication. QOL-scores and symptom grading were recorded before treatment and at 3- and 12-months of follow-up. Twenty-nine patients from the endoscopic group and 27 patients from the operative group were available at follow-up. QOL scores showed a substantial and similar increase for both groups after treatment. Symptoms of heartburn, regurgitation, and asthma were significantly improved in the endoscopic group, whereas laparoscopic fundoplication was more effective in controlling symptoms of heartburn and regurgitation compared to the endoscopic procedure. The authors concluded that endoscopic plication and laparoscopic fundoplication resulted in significant symptom improvement with similar QOL scores in a selected patient population with GERD, whereas operative treatment was more effective in the relief of heartburn and regurgitation at the expense of higher short-term dysphagia rates. Small sample size and lack of long-term follow-up limit the validity of these conclusions.

Other clinical trials regarding endoscopic plicator or suturing are limited to observational case series that do not allow for conclusions about durability and long-term effectiveness (Birk et al., 2009; von Renteln et al., 2009).

There were no peer-reviewed published studies that evaluated ESD/Sew-Right (an endoscopic/plication suturing technique).

EsophyX™ System with SerosaFuse™ Fastener (Transoral Incisionless Fundoplication Procedure)

In a RCT, Svoboda et al. (2011) evaluated the safety and efficacy of the Natural Orifice Transluminal Surgery (NOTES). Patients indicated for surgery of GERD were randomly assigned to transoral incisionless fundoplication (TIF group, n=34) and a control group, in which patients underwent the gold standard Nissen laparoscopic fundoplication (NLF group, n=18). For TIF, the Plicator method was initially used for 18 patients. During the last 2 years, the EsophyX method was used for 16 patients. The TIF and NLF procedures demonstrated similar efficacy at 3 and 12 months. The length of hospital stay was significantly shorter in the TIF group than in the NLF group. The TIF procedure appeared to be safe and comparable; one serious adverse event in the TIF group and three in the NLF group were observed. The authors concluded that both the NOTES TIF procedures are safe and effective methods for treatment of GERD, notably reducing the length of hospital stay. The effect of both procedures was sustained over 12 months. According to the authors, longer follow-up is necessary to verify the durability of efficacy. This study is also limited by a small sample size and the variable methods used to conduct TIF (both Plicator and EsophyX).

Cadiere et al. (2008) evaluated a TIF procedure using the EsophyX system in a prospective multicenter trial of 86 patients with GERD. Serious adverse events consisted of two esophageal perforations upon device insertion and one case of postoperative intraluminal bleeding. At 12 months, aggregate (n = 79) and stratified Hill grade I tight (n = 21) results showed 73% and 86% of patients with ≥50% improvement in GERD health-related quality of life (HRQL) scores; 85% discontinuation of daily PPI use and 81% complete cessation of PPIs; 37% and 48% normalization of esophageal acid exposure; 60% and 89% hiatal hernia reduction; and 62% and 80% esophagitis reduction, respectively. Resting pressure of the lower esophageal sphincter (LES) was improved significantly by 53%. According to the investigators, EsophyX-TIF cured GERD in 56% of patients based on their symptom reduction and PPI discontinuation. Study limitations included lack of a comparison group, small sample size, and short length follow-up.

Frazzoni et al. (2011) assessed reflux parameters before and after EsophyX or laparoscopic fundoplication and their relationship with symptoms in refractory GERD in 10 patients. The investigators found that in patients with refractory GERD, EsophyX fundoplication is significantly less effective than laparoscopic fundoplication in improving reflux parameters and in inducing symptom remission.

Hoppo et al. (2010) performed a small prospective study to evaluate safety and efficacy of the TIF procedure using the EsophyX system in 19 consecutive patients for the surgical treatment of GERD. At a mean 10.8 months follow-up, 5/19 had completely discontinued PPIs, and 3/19 had decreased their PPI dose. However, 10/19 had been converted to laparoscopic fundoplication for recurrent reflux symptoms and an endoscopically-confirmed failed valve. Nine of 17 were dissatisfied with the outcome, and eight were satisfied. Thirteen of 19 (68%) were considered to have been unsuccessful. According to the authors, at short-term follow-up, the TIF procedure is associated with an excessive early symptomatic failure rate, and a high surgical re-intervention rate. The authors conclude that this procedure should not be performed outside of a clinical trial.

Repici et al. (2010) evaluated the short- and mid-term clinical results of endoluminal fundoplication (ELF) with EsophyX in 20 patients. Within the first year following ELF, four patients underwent a laparoscopic fundoplication because of persistent symptoms. One patient was lost to follow-up between 6 and 12 months. Among the other 15 patients who completed 12 months follow-up, the GERD health-related quality of life (HR-QOL) score decreased from a median of 40 to 10, and 7 patients were avoided proton pump inhibitors. An improvement in esophageal acid exposure was recorded in 16.6% of patients, while in 66.7%, it worsened. The investigators concluded that ELF induced improvement of GERD symptoms and patient QOL with a reduced need for medication, in a select subgroup of patients. However, the procedure did not significantly change esophageal acid exposure in these patients. The need for revision standard laparoscopic fundoplication was high.

In a review article, Zagol and Mikami (2011) evaluated transoral fundoplication devices (included EndoCinch, NDO Plicator, Esophyx, and Stretta) for GERD that have been commercially available within the last 5 years. Both blinded and unblinded randomized studies were evaluated. Reviews of all studies with greater than 20 patients were evaluated to assess the efficacy and safety of transoral fundoplication devices. These endoluminal devices were primary matched against sham procedures. The EndoCinch and Stretta procedures were the only devices compared to laparoscopic fundoplication, the current standard for surgical management of GERD. The authors concluded that endoluminal treatment of GERD has been shown to be safe and effective in recent studies. However, the authors indicated that more RCTs need to be carried out to determine if endoluminal therapies will be a durable option for patients with GERD.

Bell and Freeman (2011) retrospectively evaluated the efficacy and safety of a rotational/longitudinal esophagogastric transoral incisionless fundoplication (TIF) in 37 patients on antisecretory medication, and with proven gastroesophageal reflux and limited hiatal hernia. Five patients were re-operations for failed laparoscopic fundoplication. The authors concluded that rotational/longitudinal esophagogastric fundoplication using the EsophyX device significantly improved symptomatic and objective outcomes in over 70% of patients at median 6-month follow-up. According to the authors, limitations of this study include ~~its~~ retrospective study design an incomplete data set for all patients, and the short 6-month duration of follow-up.

A feasibility study that included 19 patients evaluated the safety and initial efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD. The results at 1 year (n = 17) indicated that TIF was safe and had a significant effect on reducing GERD symptoms, PPI usage, acid exposure, and small hiatal hernia (Cadiere et al., 2008b). A follow-up study evaluated the long-term safety and durability of TIF. Fourteen patients completed the 2-year follow-up assessment tests. Global assessment of all outcomes in each patient revealed that 79% of patients experienced complete cure (29%) or remission (50%) of GERD at 2 years after TIF (Cadiere et al., 2009). Study limitations included lack of a comparison group and small sample size.

In a retrospective study, Barnes et al. (2011) evaluated clinical outcomes in 110 consecutive GERD patients who underwent TIF. At a median 7-month follow-up, typical and atypical symptom scores were normalized in 75% to 80% of patients and PPIs were completely discontinued by 93% of patients. According to the authors, these results supported the safety and efficacy of TIF. However, the retrospective study design, the lack of a control group, and the short term follow up limits the validity of these study results.

Other clinical trials for EsophyX are limited to observational case series that do not allow for conclusions about durability and long-term effectiveness (Trad et al., 2012; Narsule et al., 2012; Testoni et al., 2012; Demyttenaere et al., 2010; Testoni et al., 2010).

In 2011, the Agency for Healthcare Research and Quality (AHRQ) issued an update to a 2005 research review that compared evidence of the different management options for adults with Gastroesophageal reflux disease (GERD). The report evaluated three endoscopic procedures: the EndoCinch Suturing System, Stretta, and EsophyX. Similar to the 2005 comparative effectiveness review, the authors found no study of direct comparisons between the different endoscopic treatments. They found little or no difference between EndoCinch and sham, and between Stretta and sham. The strength of evidence for five cohort studies assessing the efficacy of EsophyX was rated either low or insufficient. According to the authors of the report, better quality studies with longer follow-up are needed to determine the value of endoscopic procedures in the treatment of chronic GERD (Ip et al. 2011).

Summary
The overall quality of the evidence is very low since the available studies lack adequate control or comparison groups, and have small populations, and inadequate follow-up times. Additional well-

designed, independent comparative clinical trials with long-term follow-up are required to further evaluate the GERD plication procedure using the EsophyX/SerosaFuse system (Hayes, 2011).

Polymer Injection and Implantation Techniques

Gatekeeper, Plexiglas, and Durasphere

No new studies that provide substantial new evidence regarding polymer injection and implantation techniques were identified in the most recent literature search.

In a nonrandomized uncontrolled study, Ganz et al. (2009) assessed the long-term safety and effectiveness of Durasphere (Carbon Medical Technologies), an injectable bulking agent, in the treatment of mild **to** moderate GERD. Nine patients completed the 12-month trial. There were no adverse events. The procedure was well tolerated with minimal patient discomfort and no dysphagia. At 12 months, 70% of patients discontinued all antacid medication completely and 90% of patients reduced PPI use by greater than 50%. There were no reports of esophagitis (at 12 months), erosion, ulceration, or sloughing of material at any injection site. The Durasphere material did not appear to migrate. The authors concluded that Durasphere appears to be a promising new injectable bulking agent for the treatment of mild to moderate GERD, with demonstrable efficacy and no significant adverse events in a small cohort of patients. Study limitations include nonrandomized study design without a control group and small number of subjects.

In a RCT employing sham controls, Fockens et al. (2010) assessed whether endoscopic implantation of an injectable esophageal prosthesis, the Gatekeeper Reflux Repair System (GK), is a safe and effective therapy for controlling GERD. A total of 204 patients were randomized to one of three groups: lead-in (n=60); GK (n=96); and sham (n=48). The sham patients were allowed to cross over to the GK treatment arm or exit the study at 6 months. A planned interim analysis was performed after 143 patients were enrolled, and the GK study was terminated early due to lack of compelling efficacy data. Four reported serious adverse events had occurred (2 perforations, 1 pulmonary infiltrate related to a perforation, and 1 severe chest pain) at the end of the study with no incidence of mortality or long-term sequelae. Heartburn symptoms had improved significantly at 6 months compared with baseline in the GK group and the sham group, but there were no significant between-group differences. Similarly, esophageal acid exposure had improved significantly at 6 months compared with baseline in the GK group and the sham group, but there were no significant between-group differences. The investigators concluded that the GK procedure was associated with some serious, but infrequent complications. No statistically significant differences in outcomes were observed between the treatment and control groups at 6 months.

Chen et al. (2009) conducted a systematic review that included 33 studies examining 7 endoscopic procedures (Stretta procedure, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas) Of the three procedures that were compared with sham controls (Stretta procedure, Bard EndoCinch and Enteryx), patient outcomes in the treatment group were either as good as, or significantly better than, those of control patients in terms of heartburn symptoms, QOL, and medication usage. However, for the two procedures that were compared with the laparoscopic fundoplication (Stretta) procedure and the Bard EndoCinch device, outcomes for patients in the endoscopic group were conflicting. Some patients in the endoscopic group experienced comparable outcomes as patients undergoing the laparoscopic approach, while others experienced inferior outcomes. The authors concluded that there is insufficient evidence to determine the safety and efficacy of endoscopic procedures for GERD, particularly over the long term (Chen et al., 2009).

LINX Reflux Management System

Ganz et al. (2013) conducted a nonrandomized uncontrolled study (n=100; 52% men; median age, 53 years, range 18-75) in patients with a history of GERD for at least 6 months and who had experienced a partial response to PPI treatment. The primary outcomes were normalization of esophageal acid exposure or a ≥50% reduction in acid exposure at 1 year of follow-up.

Secondary outcomes were 50% reduction in the QOL score compared with the score without PPIs at baseline. The esophageal sphincter device was implanted using standard laparoscopy by surgeons with experience with fundoplication. Normalization of or at least a 50% reduction in esophageal acid exposure was achieved in 64% of all patients (64/100). Secondary outcomes of a 50% reduction in the QOL score compared with the score without PPI at baseline was achieved in 925 of all patients (92/100). Post-hoc analysis demonstrated a reduction of ≥50% in the average daily dose of PPI was observed in 93% of all patients (93/100). Six patients experienced serious adverse effects, 4 of whom required removal of the device. In 3 patients, the device was removed at various time points following implantation because of persistent dysphagia. The most frequently reported adverse effect was dysphagia occurring in 68% of all patients. At 1 year, 11% of patients reported persistent and ongoing dysphagia. The preliminary and positive results of this study are hampered by the poor quality design, which includes lack of an adequate control or comparator group, and lack of randomization and blinding.

Bonavina et al. (2010) conducted 1- and 2-year evaluations of a feasibility trial to assess the safety and efficacy of a laparoscopically implanted sphincter augmentation device (LINX Reflux Management System) in 44 patients with GERD. Complete cessation of PPI use was reported by 90% of patients at 1 year and by 86% of patients at 2 years. One device was laparoscopically explanted for persistent dysphagia without disruption of the anatomy or function of the cardia. There were no device migrations, erosions, or induced mucosal injuries. At 1 and 2 years, 77% and 90% of patients, respectively, had a normal esophageal acid exposure. According to the authors, the new laparoscopically implanted sphincter augmentation device eliminates GERD symptoms without creating undue side effects and is effective at 1 and 2 years of follow-up. Further research with a larger patient population is needed to confirm these preliminary results and determine the clinical relevance of these findings.

As a follow-up to the Bonavina et al. (2010) study, Lipham et al. (2012) evaluated 44 patients who underwent a laparoscopic surgical procedure for placement of the LINX System. Each patient's baseline GERD status served as the control for post implant evaluations. For esophageal acid exposure, the mean total % time pH < 4 was reduced from 11.9 % at baseline to 3.8 % at 3 years, with 80 % of patients achieving pH normalization. At ≥4 years, 100% of the patients had improved QOL measures for GERD, and 80% had complete cessation of the use of PPIs. There have been no reports of long-term device-related complications such as migration or erosion. The authors concluded that sphincter augmentation with the LINX Reflux Management System provided long-term clinical benefits with no safety issues. According to the authors, patients with inadequate symptom control with acid suppression therapy may benefit from treatment with sphincter augmentation. Limitations of the study include the lack of controls and a small sample size.

Bonavina et al. (2008) conducted a multi-center feasibility trial to evaluate safety and efficacy of a magnetic sphincter augmentation (MSA) device. Over a 1-year period, 38 out of 41 enrolled patients underwent implantation of this device. The mean follow-up was 209 days. At 3 months post-operatively, 89% of patients were no longer taking anti-reflux medications and 79% of patients had a normal 24-hr pH test. Mild dysphagia occurred in 45% of patients. No migrations or erosions of the device occurred. The authors concluded that laparoscopic implant of the MSA device is safe and well tolerated. It requires minimal surgical dissection and a short learning curve compared to the conventional Nissen fundoplication. The small study population limits the validity of the conclusion of this study.

In 2011, the National Institute for Health and Clinical Excellence (NICE) issued an interventional procedure guidance document for Endoluminal Gastroplication for GERD, indicating that the current evidence suggests that there are no major safety concerns associated with endoluminal gastroplication for GERD. According to NICE, evidence from a number of randomized controlled trials (RCTs) shows a degree of efficacy in terms of reduced medication requirement in the short term, but changes in other efficacy outcomes are inconsistent and there is no good evidence of sustained improvement in oesophageal pH measurements. Therefore, this procedure should only

be used with special arrangements for clinical governance, consent and audit or research (NICE, 2011).

Professional Societies

American Gastroenterological Association (AGA): In a position statement published in 2008, the AGA assigned a grade of "Insufficient" regarding the use of current and commercially available endoluminal antireflux procedures for the management of patients with an esophageal syndrome. The AGA provides no recommendation since there is insufficient evidence to recommend for or against its use (AGA, 2008).

American Society for Gastrointestinal Endoscopy (ASGE): In a 2007 guideline on the role of endoscopy in the management of GERD, ASGE states that the endoluminal treatment of GERD is evolving and may have the potential to decrease the need for long-term antisecretory medications in selected patients (ASGE, 2007). However, most studies of endoluminal therapies for GERD have involved small numbers of PPI-dependent patients and have provided relatively limited follow-up information, so the durability of these therapies remains in question. Additionally, both short and long-term safety issues surrounding the endoluminal devices continue to be a concern. The new endoscopic antireflux techniques represent a rapidly evolving area of GI endoscopy, but additional research is needed before they can be widely recommended. Appropriate patient selection and endoscopist experience should be carefully considered before pursuing these therapies. It is important that patients and practitioners alike be aware of the limitations in the evidence that exist with these devices at the present time.

American College of Gastroenterology (ACG): In 2013, the ACG published practice guidelines regarding the diagnosis and management of GERD. They state that the "usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy." This recommendation is considered conditional, based on a moderate level of evidence (Katz et al., 2013).

The Society for Surgery of the Alimentary Tract (SSAT): SSAT (2009) has examined endotherapy for GERD and made the following recommendations:

> **"**There is a need for randomized controlled trials of sufficient size to understand the true effectiveness of all of the endoscopic therapies for GERD, and to demonstrate long term durability. Current data suggest that there are no definite indications for endoscopic therapy of GERD at this time. Physicians and patients considering endotherapy of GERD need to be aware of the limitations of the data currently, and should consider endotherapy only within the confines of a well-designed clinical trial.**"**

American Society of General Surgeons (ASGS): In April 2011, the ASGS published a position statement regarding the use of TIF stating that it supports the use of TIF in patients with symptomatic chronic GERD who are not responsive to a standard dose of PPI therapy (ASGS, 2011). The ASGS also supports its use for patients who wish to avoid lifetime drug therapy for this condition. The ASGS also supports the adoption of the procedure by trained general surgeons as a less invasive alternative to more conventional surgical techniques, stating that the preferred surgical technique should be based on the discretion and judgment of the surgeon and the patient's clinical circumstances. While the ASGS issued a favorable position statement for TIF, their recommendation does not appear to be based on a comprehensive or systematic review of the evidence.

Society of American Gastrointestinal and Endoscopic Surgeons (SAGES): In 2013, SAGES published clinical guidelines regarding endoluminal treatments for GERD (SAGES, 2011). The guideline recommends that although long term data is not yet available, EsophyX may be effective over the short term (6 months to 2 years) in patients with a hiatal hernia with typical or atypical GERD. Additional evidence is required to define optimal techniques and establish appropriate patient selection criteria, and to further evaluate the safety of the device and

technique. This recommendation was based on a weak quality of evidence. The guideline states that Stretta is considered an appropriate therapy for patients treated for GERD who are adults, age 18 years or older, with symptoms of heartburn, regurgitation, or both for 6 months or longer, who have been partially or completely responsive to anti-secretory medication therapy, and who have declined the option of laparoscopic fundoplication. This recommendation is based on a strong quality of evidence.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Several endoscopic antireflux (endoluminal) procedures have received approval by the U.S. Food and Drug Administration (FDA) for treatment of gastroesophageal reflux disease (GERD).

The Stretta System (Mederi Therapeutics) was approved in April 2000 for radiofrequency thermal ablation treatment of GERD. Additional information available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/K000245.pdf. Accessed August 29, 2013.

The Bard EndoCinch Endoscopic Suturing System (Bard Endoscopic Technologies, Billerica, MA, a subsidiary of C.R. Bard Inc), was approved in January 2001 for endoscopic suturing in the treatment of GERD. Additional information available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/k003956.pdf. August 29, 2013.

The NDO Surgical Endoscopic Plication System was approved in 2007 for endoscopic suturing in the treatment of GERD in patients who require and respond to pharmacological therapy. Additional information available at: http://www.accessdata.fda.gov/cdrh_docs/pdf7/K072125.pdf. Accessed August 29, 2013.

The current generation of EsophyX, EsophyX2, was cleared for marketing as substantially equivalent to the original EsophyX system with minor changes in November 2009 under the U.S. Food and Drug Administration's (FDA) 510(k) process. The original system was cleared for marketing in September 2007 as substantially equivalent to the predicate devices NDO Surgical Endoscopic Plication System, Bard EndoCinch, and EGS StomaphyX Endoluminal Fasteners and Delivery System. According to the approval summary letter, EsophyX2 is indicated for:

- use in transoral tissue approximation,
- full-thickness plication and ligation in the GI tract,
- the treatment of symptomatic chronic gastroesophageal reflux disease in patients who require and respond to pharmacologic therapy,
- narrowing of the gastroesophageal junction, and
- reduction of hiatal hernia <2 cm in patients with symptomatic chronic gastroesophageal reflux disease.

See the following Web sites for more information:
http://www.accessdata.fda.gov/cdrh_docs/pdf7/K071651.pdf Accessed August 29, 2013.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?db=PMN&id=k092400. Accessed August 29, 2013.

These products are Class II devices (moderate risk) deemed substantially equivalent to other endoscopic devices utilizing other procedures.

Enteryx™, a biocompatible liquid polymer, received FDA approval in 2003 through the premarket approval (PMA) process for the treatment of symptomatic GERD. However, on September 22, 2005, Boston Scientific Corporation issued a recall of Enteryx due to the device polymerizing shortly after injection into a spongy material that cannot be removed. Serious adverse events involved unrecognized transmural injections of Enteryx into structures surrounding the esophagus, potentially resulting in serious injury or death. See the following Web site for more information:

http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm064523.htm Accessed August 29, 2013.

Gatekeeper, which was expected to gain FDA approval, was withdrawn in late 2005 before approval and is not expected to be marketed.

Torax Medical obtained FDA Premarket Approval in March 2012 to market the LINX Reflux Management System. According to documents submitted to FDA, the device is intended for people diagnosed with gastroesophageal reflux disease who continue to have chronic symptoms, despite the use of maximum medical therapy for the treatment of reflux. See the following Web sites for more information:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=17882 Accessed August 29, 2013.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM286243.pdf Accessed August 29, 2013.

Additional Products
Endoscopic Suturing Device® (ESD; Wilson-Cook Medical), also called Sew-Right; Enteryx™ Procedure Kit (Boston Scientific Corp); Gatekeeper™ Reflux Repair System (Medtronic Inc); Plexiglas (polymethylmethacrylate [PMMA]) (RGmbH & Co KG)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for endoscopic therapies for the treatment of gastroesophageal reflux disease (GERD) includes Stretta procedure, the Bard® EndoCinch™ Suturing System, Plicator™, Enteryx™

Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Stretta Procedure, Endoscopic Treatment of GERD, Noncovered Procedures - Endoscopic Treatment of Gastroesophageal Reflux Disease (GERD), Non-Covered Services and TRANSORAL INCISIONLESS FUNDOPLICATION.

(Accessed August 21, 2013)

APPLICABLE CODES

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

CPT® Code	Description
43257	Esophagogastroduodenoscopy, flexible, transoral; with delivery of thermal energy to the muscle of lower esophageal sphincter and/or gastric cardia, for treatment of gastroesophageal reflux disease
43499	Unlisted procedure, esophagus
43999	Unlisted procedure, stomach

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
03/21/2014	• Removed reference link to policy titled *Wireless Capsule Endoscopy (*retired 01/01/14)
01/01/2014	• Updated list of applicable CPT codes to reflect annual code edits (effective 1/1/2014); revised description for 43257 • Archived previously policy 2013T0322L